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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Intellectual Property Group
MILLENNIUM PHARMACEUTICALS, INC.
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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,173	MEYERS, RACHEL	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 25-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,26-28 and 30-42* is/are rejected.

7)☒ Claim(s) *2,25 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 10/05/04. The amendment has been entered. Claims 1-3,6 and 25-42 are currently pending in the application and are examined herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26, 30 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites, "The isolated nucleic acid of claim wherein the nucleic acid..." It is noted that the claim does not specifically refer to any specific claim (i.e., the specific claim that claim 26 is intended to depend on is not indicated). As such, the claim is indefinite. Claims 30 and 35 are rejected for being dependent claims.

Claim Rejections - 35 USC § 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6, 26-28, 30, 31, 33, 35, 36, 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

An isolated 47324 nucleic acid molecule selected from a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1; and b) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 3, as well as a vector comprising said isolated nucleotide sequence(s) and an isolated host cell comprising said isolated nucleotide sequences;

does not reasonably provide enablement for the full scope of the instant claims. Specifically, the instant claims are not enabled for any nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2, a host cell comprising any nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2, a method of producing said amino acid sequence, and a non-isolated host cell comprising said isolated nucleic acid sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to an isolated 47324 nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO: 2, which includes the nucleic acid sequences that are SEQ ID NO: 1 (a full length cDNA encoding SEQ ID NO: 2, including untranslated regions) and SEQ ID NO: 3 (only the coding sequence of the cDNA encoding SEQ ID NO: 2), as well as a vector comprising said sequence(s), a host cell comprising said nucleic acid sequence(s) and methods for making the polypeptide that is SEQ ID NO:2 using the nucleic acid(s)/cell. Therefore, the general nature of the invention is biotechnology.

The breadth of the claims

The broad claims encompass any isolated nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 2, as well as a vector comprising said nucleic acid sequence, a host cell comprising said nucleic acid sequence (which includes a non-isolated cell, such as a cell in a subject), and methods of making the polypeptide using the nucleic acids/cell.

Working Examples and Guidance in the Specification

The instant application discloses that the mRNA corresponding to SEQ ID NO: 1 exhibits altered expression in certain cell types. For instance, real-time PCR was used to identify that the mRNA corresponding to SEQ ID NO: 1 was significantly overexpressed in lung tumor cells compared to normal lung cells, as well as in prostate cancer cells compared to normal prostate cancer cells, etc. (e.g., the specification discloses the expression levels of SEQ ID NO: 1 mRNA in a plethora of cell types, some of which show altered expression of SEQ ID NO: 1 mRNA). It

is noted that the real-time PCR is only indicative of the mRNA levels, and not necessarily indicative of the level of protein encoded by the mRNA. As such, the disclosure indicates utility for the claimed nucleic acids. However, regarding enablement, the specification only provides enablement for the isolated nucleic acid sequences comprising SEQ ID NO: 1 and 3 (and vectors and isolated cells comprising said nucleic acids) for their use in diagnosing specific cancers (such as lung cancer and prostate cancer, as indicated above). There is no disclosure provided which indicates that the protein levels (of SEQ ID NO: 2) are commensurate with the corresponding mRNA levels, which would be required in order for the protein levels to be diagnostic indicators of cancer, etc. Furthermore there is no specific activity/function disclosed for the amino acid sequence of SEQ ID NO: 2.

It is noted that the claims encompass a non-isolated cell comprising the isolated nucleic acid sequences. Given the broadest reasonable interpretation, these claims encompass a transgenic animal wherein the cell is a transgenic cell in the transgenic animal. There is no disclosure provided that indicates the applicants have made a transgenic animal comprising the isolated nucleic acid sequences. Furthermore, there is no specific guidance provided on how to make said transgenic animals, nor is there a specific phenotype disclosed for the transgenic animals

The unpredictability of the art and the state of the prior art

The relevant art indicates that nucleic acid expression is not necessarily indicative of the level of the encoded protein in a cell. For instance, Meric et al. (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability,

mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

Additionally, with respect to the expression of Endothelial Differentiation Gene (Edg) encoded G protein-coupled Receptors, Goetzl et al. (Cancer Research (1999) 59:5370-5375) teaches that the expression of Edg mRNA is not always indicative of the Edg protein level in the cell. Specifically, when analyzing Edg-2 and Edg-5 mRNA levels (by semiquantative RT-PCR) and protein levels (by Western blot) in normal ovarian samples (IOSE) and ovarian cancer samples (OV202), the level of Edg-2 mRNA did not appear significantly different in the samples in IOSA samples than OV202 samples. However, Edg-2 protein levels were significantly higher in the IOSA samples than the OV202 samples (e.g., see Figure 1, Figure 2, Table 1; as well as the paragraph bridging pages 5371-5372). Therefore, the mRNA level of GPCRs are not always indicative of the corresponding protein level in the cell.

It is noted that Schrader et al. (Journal of Urology, 2003; Vol. 169, pages 1858-1864) reviews the state of the art of real-time PCR and indicates that real-time PCR can be used to accurately assay the mRNA levels in a sample. Specifically, Schrader teaches, "Real-time RT-PCR is a reliable, rapid and relatively inexpensive technique that can be easily adapted for standardized preclinical and clinical applications at different centers." (See abstract). However, Schrader does not address the issue of correlating the mRNA level to the corresponding protein levels in a cell. As such, Schrader indicates the utility of real-time RT-PCR as a diagnostic indicator of mRNA levels, but does not overcome the problems recognized in the art with respect to using mRNA levels as indicators of protein levels in a sample.

With respect to any nucleic acid encoding SEQ ID NO:2, it is noted that the claims encompass sequences which are different from SEQ ID NO:1 and 3, but which still encode SEQ ID NO:2. Since the specification has disclosed that the nucleic acid of SEQ ID NO:1 and 3 can be used in diagnostic assays to identify the level of 47324 mRNA in a cell, which has been disclosed as altered in certain cell types (e.g., lung tumor cells, prostate tumor cells, liver fibrosis cells, etc.), the specification is enabling only for using sequences of SEQ ID NO:1 and 3 to assay mRNA level. However, a nucleic acid sequence which encodes SEQ ID NO: 2 encompasses nucleic acid sequences which are significantly different from SEQ ID NO:1 and 3 (based on the wobble hypothesis). The nucleic acids encompassed by the claims which are different from SEQ ID NO: 1 and 3 would encompass sequences which would not specifically hybridize to the target mRNA. As such, nucleic acid sequences encoding SEQ ID NO: 2 would not be useful in methods of determining mRNA levels in a cell. Therefore, the claims are not enabled for any nucleic acid sequence other than nucleic acids sequences comprising SEQ ID NO:1 and SEQ ID

NO: 3.

With respect to the host cells wherein the host cell can be a non-isolated cell (e.g., a transgenic cell in a transgenic animal) the prior art indicates that methods of successfully making transgenic animals is unpredictable. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for making transgenic animals is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects [see Ryan *et al.*, **Sem. Neph.** 22:154-160, 2002] can dramatically influence the phenotype of the resultant transgenic animal. Ryan *et al.* state that methods such as pronuclear injection or gene targeting by homologous recombination are still limited by several unpredictabilities, including differences in transgene copy number and position of integration into the genome. Furthermore, Ryan *et al.* states, "The location of integration can have dramatic effects on the expression of a transgene. Called the position effect, transcriptional regulatory sequences at or near the insertion site can strongly influence (the) transgene, even impart a new set of instructions." [See p. 155, 2nd column].

Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends upon the particular gene construct used, to an unpredictable extent. This is supported by Holschneider *et al.* [**Int J. Devl. Neuroscience** 18:615-618, 2000] who state that the, "knocking out or insertion of a single gene may result in no phenotypic change. This may be the case, in particular, if there exist gene redundancy mechanisms whose presence may prevent abnormal phenotypes from becoming masked. Conversely, single genes are often essential in a number of different behaviors and physiologic

processes. Hence, ablation of an individual gene may prove so drastic as to be lethal, or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interactions of the various new physiologic changes or behaviors." [See p. 615, col. 1-2]. Holschneider *et al.* discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory systems which may be activated to mask the resulting phenotype, these compensatory changes may be due to the differential expression of another gene, which may be regulated by the downstream product of the ablated gene, as well as the variability in phenotypic characterization due to particular mouse strains [see p. 616, 1st column].

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

Quantity of Experimentation

In view of the breadth of the claims and the unpredictable nature of the invention, as recognized in the art (see above) additional experimentation would have to be performed in order to make and use the claimed invention. Considering that mRNA levels are not indicative of protein levels, additional experimentation would be required in order to determine that mRNA levels are commensurate with protein levels. Furthermore, considering that the claims encompass cells in transgenic animals (i.e., non-isolated cells comprising the isolated nucleic acids), additional experimentation would be required in order to overcome the problems recognized in the art, as indicated above. Considering that the indicated art teaches that the

problems are not routine problems that can be overcome with routine experimentation, the amount of additional experimentation required is considered undue.

Level of the skill in the art

The level of the skill in the art required for biotechnology applications is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the limited amount of working examples and guidance provided in the specification, as well as the teachings of the relevant art and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Claim Objections

Claims 2 and 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 21-31 are objected to because of the following informalities: the claims start with the article "An". It is suggested that the claims be amended to start with the article "The" instead of "An" in order to clearly set forth the claims as referring the isolated nucleic of the independent claim rather than an isolated nucleic of the independent claim. Appropriate correction is required.

Allowable Subject Matter

It is noted that amending the claims to be drawn to isolated nucleic acids comprising SEQ ID NO:1 or SEQ ID NO:3, as well as vectors comprising these specific nucleic acid sequences, isolated host cells comprising these specific nucleic acid sequences. Furthermore, the Examiner will consider any evidential submission with respect to correlation of the 47324 mRNA and 47324 protein levels in the sample cells in response to this non-final action. It is noted that any evidence should be submitted prior to the close of prosecution for the Examiner's consideration.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER

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